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A Two-Step Synthesis of Terbinafine

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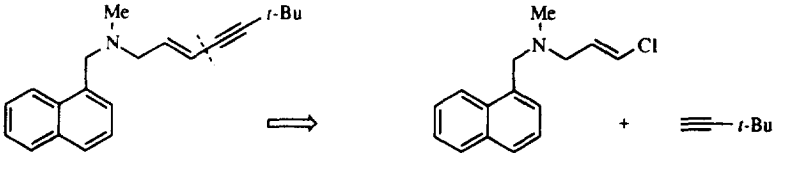
Abstract: An efficient and high yielding synthesis of terbinafine **1a** and amino enyne derivatives **1b-f** is described from amino vinyl chlorides **2a-b** and 1-alkynes in the presence of a weak ligated palladium complex: $PdCl_2(PhCN)_2$ in piperidine.

Among the antifungal agents selectively inhibiting fungal squalene epoxidase recently discovered, terbinafine **1a**, which contains the (E)-1,3-enyne structural moiety, exhibits strong antimycotic activity and is used currently for the treatment of skin mycoses.[1]

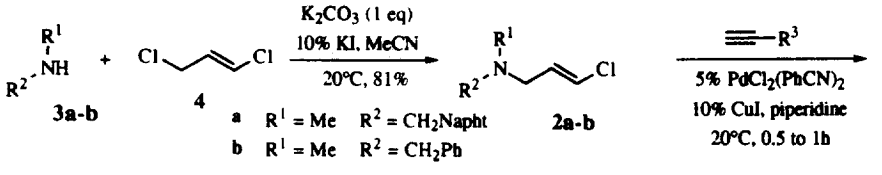
Several syntheses have been described and often lead to a mixture of regio- and stereo-mers, which are difficult to separate.[1] A stereospecific approach based on the Pd-catalyzed Stille coupling of a (E)-vinyl iodide with an alkynyl stannane was reported.[2] However, this method requires the preparation of both reagents: the vinyl iodide is formed by hydrozirconation of an alkyne with zirconocene chloride hydride which is an expensive reagent, and the alkynyl stannane is prepared by reaction of lithium acetylide with tributyl stannyl chloride at -78°C.[3] A recent publication[4] reporting the preparation of an amino enyne related to terbinafine prompts us to report our own results concerning a high yielding synthesis of geometrically pure terbinafine **1a**, from commercially available starting materials. The key step of this approach is based on the stereospecific and rapid reaction of amino vinyl chlorides with 1-alkynes which gives high yields of amino enynes **1** (86-97%) in the presence of a catalytic amount of $PdCl_2(PhCN)_2$ and CuI in piperidine[5] (scheme 1).

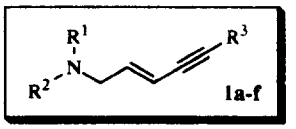


1a **2a**

Scheme 1

Thus, amination of (E)-1,3-dichloropropene **4** with N-methyl-1-naphtalene methanamine **3a** in dry acetonitrile in the presence of K_2CO_3 and a catalytic amount of KI[6] led regioselectively to the (E)-vinyl chloride **2a** in 81% yield (scheme 2).





1a-f

1	R^1	R^2	R^3	isolated yield
a	Me	CH_2Napht	*t*-Bu	93%
b	"	"	$SiMe_3$	97%
c	"	CH_2Ph	*t*-Bu	94%
d	"	"	$SiMe_3$	90%
e	"	"	$(CH_2)_2OH$	97%
f	"	"	C_5H_{11}	86%

Scheme 2

Coupling of (E)-amino vinyl chloride **2a** with *tert*-butyl acetylene in the presence of piperidine and catalytic amounts of $PdCl_2(PhCN)_2$ (5%) and CuI (10%) provided stereospecifically terbinafine **1a** in 93% isolated yield. The coupling reaction of **2a** with trimethyl silyl acetylene can also be performed in excellent yield (97%). It is noteworthy that the use of $PdCl_2(PhCN)_2$ instead of $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ improved dramatically the rate of the reaction,[5] thus the coupling reaction proceeds rapidly within 0.5 to 1h instead of 20h with $PdCl_2$,PPh_3.[4] Furthermore, the use of benzonitrile rather than triphenyl phosphine as ligand in the palladium complex simplified the purification of the products.

In a similar way, various geometrically pure allyl amine derivatives **1c-f** bearing the (E)-1,3-enyne structural moiety have been prepared in excellent yields from amino vinyl chlorides **2b**.

In conclusion, we have shown that $PdCl_2(PhCN)_2$ is the catalyst of choice for the coupling of less reactive vinyl chlorides with 1-alkynes. The efficiency of our procedure was illustrated by the high yield synthesis, under mild conditions, of terbinafine and amino enyne derivatives.

Typical procedure for the preparation of terbinafine (1a): To a suspension of $PdCl_2(PhCN)_2$ (19 mg, 0.05 mmol) in piperidine (3 mL) was added successively vinyl chloride **2a** (246 mg, 1 mmol), *tert*-butyl acetylene (123 mg, 1.5 mmol) and CuI (19 mg, 0.1 mmol). The reaction mixture was stirred at room temperature and monitored by TLC analysis until complete consumption of the vinyl chloride (0.5 to 1h). After treatment with a saturated aqueous solution of ammonium chloride and extraction with diethyl ether, the organic extract was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Filtration through silica gel (petroleum ether / AcOEt 20%) afforded 271 mg (93%) of pure terbinafine **1a**.[7]

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